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Neurocognitive course at two-year follow-up in the Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study

Running head: Neurocognitive course in NAMACO patients

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Abstract

Objective: To examine neurocognitive course over time among people with well-treated HIV.

Design: The Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study is an ongoing, prospective, longitudinal, multicenter and multilingual study within the Swiss HIV Cohort Study (SHCS). Participants undergo neuropsychological assessment at baseline and two-yearly follow-up.

Setting: Seven SHCS centers

Subjects: Patients aged ≥45 years enrolled in the SHCS with fluency in the local language (French, German or Italian) and agreeing to participate in the NAMACO study: 981 participants at baseline, 720 at two-year follow-up of whom 644 had complete data sets.

Intervention: Standardized neuropsychological assessment at baseline and two-year follow-up.

Main outcome measure: Neurocognitive performance using Frascati criteria and mean z-scores.

Results: Four participants (of 644, 0.6%) had plasma HIV-1 RNA >50 copies/mL; median CD4 count was 660 cells/μL. According to Frascati criteria, 204 participants (31.7%) had neurocognitive impairment (NCI) at baseline. NCI severity in these participants changed little over two years and comprehensive models based on Frascati criteria were not feasible. Examining mean z-scores, however, we observed neurocognitive stability or improvement over two years in five of seven neurocognitive domains assessed. Age ≥65 years (p=0.02) and cognitive complaints (p=0.004) were associated with neurocognitive decline, while black race (p=0.01) and dolutegravir treatment (p=0.002) were associated with improvement.

Conclusion: Frascati criteria were less sensitive in measuring NCI change and therefore unsuitable for following neurocognitive course in our cohort of people with well-treated HIV. Examining neurocognitive course by mean z-score change, we observed stability or improvement.

Keywords: aging, HIV, HIV-associated neurocognitive disorder, neurocognitive impairment, neuropsychological testing

Introduction

Neurocognitive impairment (NCI) has been part of the natural history of HIV since the beginning of the pandemic. HIV-associated dementia prevalence has decreased due to the availability of safe and effective antiretroviral therapy (ART). However, mild forms of NCI remain prevalent even with HIV viral suppression, affecting around 30% of people with HIV (PWH).[1,2] Multiple non-HIV-related factors have been associated with NCI, including comorbidities, opportunistic infections and depression.[3] It has been argued that high NCI prevalence may be related to over-diagnosis of cases using current diagnostic tools.[4,5] Against this, longitudinal observational studies have described progression of mild, asymptomatic to symptomatic NCI over time.[6,7]

The Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study is a longitudinal study created to explore NCI within a well-characterized and well-treated cohort of PWH aged ≥45 years old, as part of the Swiss HIV Cohort Study (SHCS).[3] We previously presented the results derived from the baseline analyses of the NAMACO study, in which we reported NCI prevalence and the main associated factors associated with NCI [3]. In the current study, we present the longitudinal analysis of NAMACO study participants, using both categorical (NCI according to Frascati criteria)[8] and continuous (annualized changes of demographically-adjusted z-scores) NCI definitions. The aim of the study was to examine NCI course over time and the main factors associated with neurocognitive performance change.

Methods

Study design and participants

The NAMACO study is an ongoing prospective, longitudinal, multicenter and multilingual (French, German and Italian) study nested within the SHCS.[3,9]

SHCS patients aged ≥45 years, followed up at one of seven cantonal hospitals in Switzerland (Basel, Bern, Geneva, Lausanne, Lugano, St. Gallen and Zurich) and with sufficient fluency in the local language (French, German or Italian) to undergo neuropsychological assessment,

were invited to participate in the NAMACO study between May 1st 2013 and November 30th 2016 (baseline). The ethics committees of each cantonal hospital center approved the NAMACO study protocol, and all patient participants signed informed consent prior to being included.[3]

A total of 981 participants were recruited at baseline and underwent formal neuropsychological assessment. They were then invited to undergo repeat neuropsychological assessment at two-year and four-year follow-up visits. The current study examined baseline and two-year follow-up data collected between May 2013 and December 2018.

Procedures

At baseline and follow-up visits, NAMACO study participants completed a neuropsychological test battery covering seven cognitive domains correlated to HIV-associated NCI based on the International Network for Strategic Initiatives in Global HIV trials (INSIGHT) Strategic Timing of AntiRetroviral Treatment (START) study[10] (Supplemental Table 1, http://links.lww.com/QAD/C268.). Assessment was conducted by trained neuropsychologists. Raw scores derived from testing were converted to a demographically-adjusted standard score (z-score). Functional impairment was assessed using Lawton's Instrumental Activities of Daily Living (IADL) and Patient's Assessment of Own Functioning Inventory questionnaire (PAOFI)[11] where impairment was defined as difficulties in at least two items out of eleven. Depressive symptoms were assessed using the Centre for Epidemiological Studies Depression Scale (CES-D)[12] where CES-D scores of 16-26 were taken to indicate risk of mild depression and scores ≥27 risk of severe depression. Cognitive complaints were assessed using the three European AIDS Clinical Society (EACS) screening questions on memory loss, mental slowing and attention difficulties.[13] For each of the three EACS screening questions, response options were: *never, hardly ever* or *yes, definitely*. Participants answering, *yes, definitely* to at least one question were considered to have cognitive complaints as previously described[14].

We examined NCI categorically using Frascati criteria[8] and continuously using mean z-scores. Using Frascati criteria, participants were classified as having no NCI, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), HIV-associated dementia (HAD), and non-HIV-associated NCI. ANI and MND were defined as ≥1 SD below mean in ≥2 cognitive domains without (ANI) or with (MND) functional impairment, and HAD was defined as ≥2 SD below mean in ≥2 cognitive domains with functional impairment. Non-HIV-associated NCI refers to NCI considered to be due to confounding conditions such as psychiatric disorders (including depression), substance use, ART toxicity and structural damage associated with neurodegenerative disorders, previous opportunistic central nervous system (CNS) infection, stroke or trauma. The NAMACO study protocol and neuropsychological assessment details have been published elsewhere.[3]

Participant clinical and demographic characteristics were obtained from the SHCS database from six-monthly SHCS visits, taking data from the SHCS visit closest in time to the neuropsychological assessment.

Outcomes

The primary outcome measures were Frascati category at two-year follow-up, as described above, and annualized mean z-score changes. Mean z-scores were calculated for baseline and two-year follow-up visits for the different neuropsychological tests across all cognitive domains. If neuropsychological tests were used for ≥1 domain they were considered only once for the mean z-score calculation. The individual z-score changes were divided by the number of years between the baseline and follow-up assessments in order to obtain annualized z-score changes. In order to investigate factors associated with Frascati definition and z-score changes, we examined demographic and HIV-related characteristics, comorbidities, ART changes and CNS penetration effectiveness (CPE) score (based on Letendre *et al*. definitions[15,16] as previously described[17]).

Statistical analysis

Analyses were performed through univariable and multivariable linear regression models. The following covariables were assessed in our univariable model: age, race/ethnicity, HIV acquisition mode, education, employment, depressive symptoms (CES-D), use of antidepressants, current intravenous and non-intravenous drug use, smoking, alcohol consumption, comorbidities (cardiovascular, metabolic, liver, kidney and bone-related), detectable viral load (HIV-1 RNA ≥50 copies/mL), CD4 and CD8 cell counts, CPE score, ART changes, hepatitis B or C virus co-infection, and opportunistic infections. We restricted our study to participants without missing values for covariables or endpoints (Frascati category and mean z-score changes) (figure 1).

The individual probabilities of dropping out of the study were obtained by multivariable logistic regression adjusted for all baseline characteristics. Univariable and multivariable linear regression models were subsequently weighted for the inverse probability of dropping out of the study. Models were built manually, adding clinical, demographic and other baseline characteristics: EACS screening questions, age ≥65 years old, black race, sex, non-intravenous drug use, depression (CES-D score ≥27 and/or antidepressant treatment), CD4/CD8 ratio and HIV-1 viral load. We then added variables with a p-value < 0.2 in univariable analyses. The basic model selection (model 1) was based on Akaike and Bayesian information criteria. In model 2, we added the CPE score changes and in model 3 we added changes in ART. Examining Frascati categories, we observed that NCI changes at two years were limited mainly to those between no NCI and ANI. As this could not be adequately modelled, we present only descriptive analyses. We used Stata IC 14.2 (StataCorp, College Station, TX) for all analyses.

Role of the funding source

The study funders had no role in study design, data collection, interpretation or writing of the article. The corresponding author had full access to all study data and final responsibility for the decision to submit for publication.

Results

Of 981 participants recruited at baseline, 720 presented for two-year follow-up of whom 644 had complete datasets (figure 1). There was no difference in clinical and demographic characteristics between these 644 participants and the 337 participants who did not attend or had incomplete datasets in terms of median age, sex, race/ethnicity, HIV acquisition mode, education, employment, HIV plasma viral load or median CD4 count. Reasons for not participating at two-year follow-up are listed in figure 1; 129/337 (48.9%) participants agreed to remain in the NAMACO study and attend four-year follow-up.

At two-year follow-up, participants had a median age of 55 years, with most (70.3%) aged 45-55 years old, and 16.3% >65 years old. The majority were male (80.8%) and white (92.4%) (table 1). Median CD4 count was 660 cells/μL and <1% of participants had detectable plasma HIV-1 RNA viremia (table 2). Comparing baseline and follow-up characteristics, there were significant differences in age (as the population aged), employment (increased retirement due to aging), detectable HIV-1 RNA viremia, detectable hepatitis C viremia in co-infected participants (eradication with treatment), and CPE score (tables 1 and 2).

We also found differences in the distribution of Frascati criteria by language-region with 48%, 72% and 57% having no NCI, and 32%, 20% and 43% having NCI, among French-, German-, and Italian-speaking centres, respectively. These differences are partly explained by sex, ethnicity, non-injecting drug use, and reported cognitive complaints as measured by EACS screening questions.

Course of NCI and cognitive domains affected

At two-year follow-up, 204 participants (31.7%) had NCI based on Frascati criteria: 126 (19.6%) with ANI, seven (1.1%) with MND, three (0.5%) with HAD, and 68 (10.6%) with non-HIV-associated NCI. NCI diagnosis changed in 149 participants (23.1%) between baseline and follow-up: 86 (57.7%) improved and 63 (42.3%) declined. Most changes occurred among participants with ANI who regained normal neurocognitive function (38.3%) and participants without NCI who developed ANI (22.1%) (figure 2, panel A and B). Among participants with non-HIV-associated NCI, the most common diagnosis was psychiatric disorders (70.6%), most frequently depression (93.8%). Of 166 participants with CES-D scores of ≥16, 48 (28.9%) were on antidepressants.

The most affected cognitive domains at follow-up were motor skills (34.5%), attention and working memory (27.3%) and speed of information processing (27.0%). We observed a significant reduction in participants with sensory and perceptual skills impairment with time (table 2). Examining mean z-score change by domain, greatest improvements occurred in speed of information processing, language, and executive function (figure 2, panel C). Functional impairment, as measured by IADL and PAOFI, was observed in 36 participants (5.59%), similar to baseline (p=0.70).

No patient died from HIV/AIDS related causes. Oncological causes were recorded for six patients (Frascati: 2 none, 1 ANI, 1 HAD and 2 other), cardiovascular causes were recorded for five patients (2 none, 1 ANI, 2 other), infectious causes were recorded for two patients (1 none, 1 other), two patients died in accidents (1 none, 1 other), two patients died of suicide (1 none, 1 ANI). For six patients the cause of death was unknown. There was a significant difference in mortality between the different Frascati diagnoses (Fisher's exact p=0.006, non-parametric test for trend p=<0.001), but when excluding non-HIV associated NCI, this difference disappeared (Fisher's exact p=0.21, non-parametric test for trend p=0.38).

Predictors of annualized z-score changes

Figure 3 shows the results of uni- and multivariable linear regression models for annualized z-score changes. Models are weighted with the inverse probability of dropping out, obtained from logistic regression with a ROC AUC of 0.7. Univariable analyses showed mean z-score decreases (neurocognitive decline) among participants aged >65 years old (p = 0.01) and those with cognitive complaints at baseline (p = 0.04). In contrast, black race and ART change were independently associated with mean z-score increases. Although the number of participants with detectable hepatitis C viremia decreased with time, there was no association between hepatitis C treatment and improved neurocognitive performance (data not shown).

Multivariable analyses were repeated with different sets of covariables starting from our initial model (model 1, figure 3, Supplemental table 2, http://links.lww.com/QAD/C268). Model 2 added CPE score changes and model 3 added ART changes to a dolutegravir-based regimen. We created model 3 because addition of dolutegravir was the most frequent treatment change we observed, occurring in 190 patients (29.5%) between baseline and follow-up, and because dolutegravir incidentally increases CPE score. After adjusting, the factors most strongly associated with annualized mean z-score decreases were cognitive complaints at baseline (-0.0416 [95% CI -0.0701 to -0.0131], p=0.004), being aged >65 years (-0.0432 [95% CI -0.0799 to -0.0064], p=0.02), and non-intravenous drug use (-0.0338 [95% CI -0.0660 to -0.0016], p=0.04) (figure 3, Supplemental table 2, http://links.lww.com/QAD/C268). Conversely, starting ART regimens containing dolutegravir was associated with mean z-score increases (0.0361 [95% CI 0.0014 to 0.0707], p=0.002). An increase in mean z-score was also observed among black race participants (0.0698 [95% CI 0.0157 to 0.1239], p=0.01).

Discussion

Among PLW aged ≥45 years with well-treated HIV followed up over two years, we have observed that the majority of change was between the diagnoses of no NCI, ANI and non-HIV-associated NCI, with a trend towards improvement. Z-scores changed without changing Frascati category, making z-scores a more sensitive means of following NCI course over time. Previous cognitive complaints, aging and non-intravenous drug use were associated with a decrease in z-scores, while black race and ART changes to dolutegravir were associated with an increase. Annualized changes in z-scores across all neurocognitive domains, whilst small, were towards improvement.

The continued use of Frascati criteria[8] in diagnosing HIV-associated NCI is a subject of controversy. A limitation of these criteria is the risk of false positive cases, arising from the large number of neuropsychological tests performed and the assumption that resulting z-scores follow a normal distribution which increase the odds of diagnosing ANI by chance.[4,5] In the current study, the most prevalent diagnosis at two-year follow-up was ANI (19.6%, compared to 24.5% at baseline). Only three participants developed HAD during the same period, two previously diagnosed with ANI and one previously diagnosed with MND. Few studies have examined the course of ANI. Grant and co-authors reported the course over a median of 45 months of 347 patients enrolled in the CHARTER study who had no NCI or were diagnosed with ANI at baseline. They observed that patients with ANI had a two- to six-fold increased risk of developing symptomatic NCI, based on self-reports (IADL and PAOFI) and performance-based tests.[7] However, the CHARTER study population is not comparable to ours, as participants had different demographic characteristics and higher prevalence of detectable viremia.[6,7] In contrast, Cole and co-authors of the Multicenter AIDS Cohort (MAC) study, addressing long-term psychomotor performance prior to the arrival of new ART, found that neuropsychological evaluations remained stable after five years.[18] In our study among PLW with well-treated HIV, the follow-up period, at two years, is relatively short and the z-score changes we observed in individual cognitive domains and overall were small. This suggests that follow-up needs to continue over a longer period if marked changes in z-scores, or indeed clinically-perceptible differences, are to occur. Although z-score changes were associated with clinical, demographic and treatment characteristics of our population, our follow-up period was shorter than the CHARTER and MAC study follow-up periods.[7,19] If NCI course is slow, we would not notice deterioration at the two-year follow-up time point of our study. Analyses of the four-year follow-up data will shed light on this.

The EACS screening questions[13] are part of the standard SHCS clinic visit. Previous studies have reported a weak association between these questions and NCI.[20,21] From baseline NAMACO study data, we reported low positive and negative predictive values of the EACS screening questions for the diagnosis of NCI.[14] In the current study, we looked for a longitudinal effect, defining NCI according to both Frascati criteria and mean z-scores to avoid possible errors by chance driven by ANI diagnosis. As self-reported tools could be

indirect markers of depression,[22] and although our models were adjusted for depression, we looked for associations excluding participants with CES-D scores >27 and those on anti-depressants. The association between answering, *yes, definitely* to at least one EACS screening question and NCI remained unchanged whether we examined Frascati categories (taking NCI as a dichotomous variable where ANI, MND, HAD and non-HIV-associated NCI were grouped as NCI against *no NCI*) or mean z-scores. In summary, and contrary to previous publications, we did find an association between previous cognitive complaints and decreased neurocognitive performance at follow-up, even when adjusting for depression. Our hypothesis is that the EACS questions could reflect risk of subsequent neurocognitive decline rather than immediate neurocognitive performance.

Unsurprisingly, we noted a negative effect of aging on neurocognitive performance. There is no clear evidence for a putative accelerated decline of neurocognitive function in PWH.[1,19,23,24] Authors from the MAC study reported that the association between NCI and aging in HIV patients is not a linear process, with accelerated or natural decline being a consequence of multiple factors but with AIDS being the main driver for premature aging.[25] If we consider this non-linearity, and assume different paths according to each patient's characteristics (viral load, CD4 count, opportunistic infections), we could expect a natural neurocognitive decline in our well-treated population, as HIV-effects are neutralized. Non-intravenous drug use was also associated with decreased neurocognitive performance in our study. Non-intravenous drug use has been observed to be associated with possible confounding factors such as co-medication with agents producing neurocognitive adverse effects,[26] depression and anxiety disorders.[27] It is possible that HIV and substance misuse work synergistically, affecting different neurological pathways, thus contributing to a double burden that leads to further cognitive deterioration.[26]

We observed that black race and ART changes to dolutegravir were associated with improved neurocognitive performance. Regarding black race, although an improvement in z-scores was observed, participants were still underperforming, as their mean z-score was negative (impaired) at both visits. Although most participants of black race were African, to our knowledge there is no evidence for ethnicity/race differences in the psychological tests we used which would explain our results. Black participants had lower rates of confounding factors (smoking, alcohol and drug consumption) compared to non-black participants, and high levels of undetectable viremia. To put our observations into perspective, the observed improvement was derived from performance in a single domain, sensory and perceptual skills, and this, in a small number of patients, is difficult to interpret. Of note, the improvement observed was not associated with antidepressant treatment. Regarding ART changes, we observed a decrease in use of the non-nucleoside reverse transcriptase inhibitor efavirenz, favoring dolutegravir use, and participants newly-treated with dolutegravir had improved neurocognitive performance. Although decreased efavirenz use was driven mainly by the fact that dolutegravir was part of new simplified treatment options, stopping efavirenz was listed by treating clinicians as being due to neurological or neuropsychological adverse effects in 26% of cases. Neuropsychiatric adverse effects associated with efavirenz have been widely described.[28,29] However, when analyzing neurocognitive performance in NAMACO

participants with these complaints, most did not have NCI, and their main complaints were sleep deprivation and dizziness. As dolutegravir has the highest possible CPE score (four),[17] its increased used possibly explains the trend towards neurocognitive improvement observed with higher CPE scores (figure 3). We consider the improved neurocognitive performance in participants switched to dolutegravir as being due to an effect of clinical practice, as dolutegravir was the most common ART addition in our population (183 participants). Hence, as we observed a global trend towards improvement, new participants on dolutegravir will also follow this course. To support this argument, participants without ART changes also improved neurocognitive performance. We stress that the impact of dolutegravir use needs further investigation, especially in the long term, and that our study was not powered to show that dolutegravir prevents NCI in our population.

Our study has limitations. We have a considerable attrition bias due to the high lost to follow-up rate, which we attempted to account for by weighing our models. Most participants with HAD at baseline (four) were lost to follow-up at two years, which limits our understanding of factors associated with this group. Moreover, as men who have sex with men and Caucasians were over-represented, there is potential recruitment bias. We also found differences in neurocognitive performance by centres that can only be partially explained by some covariables in our models. These differences were also observed by language region, suggesting that the language used for the neuropsychological assessment could play a role in these differences. However, as mean z-score change differences between baseline and follow-up were not large, and as by Frascati criteria we observed a trend to stability, we do not consider that language differences affected our study results. One of the strengths is that the NAMACO study represents the neurocognitive status of PWH aged ≥45 years old throughout Switzerland. As our study recruited not only patients with previous cognitive complaints but also those without complaints, we can study NCI incidence as well as NCI course. As NAMACO study participants have well-treated HIV, we can examine HIV-associated NCI in the 'best-case' treatment scenario. Our neuropsychological test battery was performed by trained neuropsychologists rather than via computer so that participants with no computer skills could still be included. Finally, our assessment was performed in three languages (French, German and Italian) to enable the majority of participants to be assessed in their native language.

In conclusion, we found that neurocognitive performance in a well-treated population of PWH aged ≥45 years old remains generally stable or improved at two-year follow-up. We did not observe that ANI was a portal into more severe NCI but, on the contrary, was associated with stable or even improved cognition over time. As a consequence of this stability, we consider that Frascati criteria have limitations when analyzing NCI course in populations of PWH with low prevalence of non-ANI categories. These findings raise questions about the value of stigmatizing PWH with alleged cognitive deficits when they are asymptomatic. Analysis of our four-year follow-up data will help address these questions. Finally, the factors we observe to be associated with NCI in our population suggest that adequate HIV treatment significantly decreases the chances of NCI incidence or progression.

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Author contributions: R.DP., and MC designed the study, and performed and supervised clinical and/or experimental aspects of the study. B.L performed statistical analyses, and interpretation of study results. J.D performed statistical analyses, interpretations of study results, and wrote the first draft of the manuscript. KEAD., performed and supervised clinical and/or experimental aspects of the study, and participated in manuscript preparation. I.N., P.E.T., M.S., U.K., C.H., K.G., A.C., F.A., P.S., T.H., C.DB., S.R., B.H., L.S. performed and supervised clinical and/or experimental aspects of the study. All authors participated in the final revisions of the manuscript and agreed its submission.

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Figures legends

Figure 1. Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study design IADL, Instrumental Activities of Daily Living; PAOFI, Patients' Assessment of Own Functioning Inventory; CES-D, Centre for Epidemiologic Studies Depression scale; EACS, European AIDS Clinical Society.

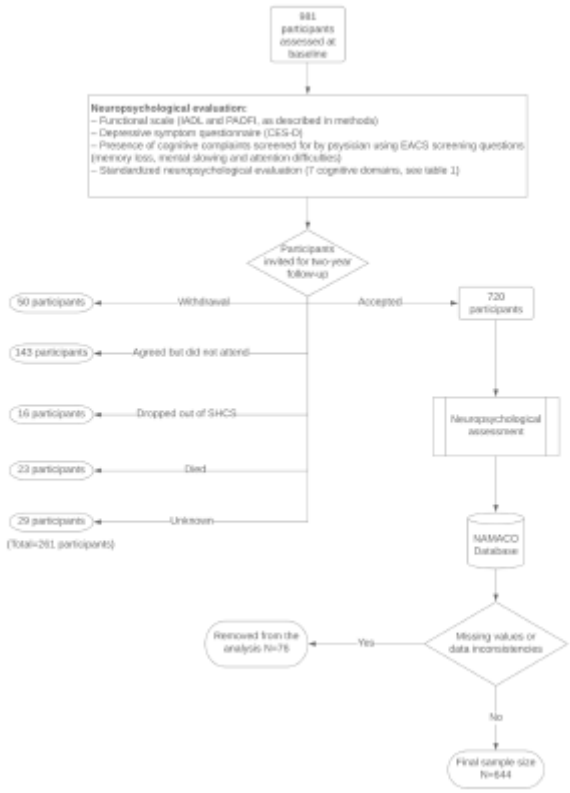

Figure 2. Panel A: Changes in neurocognitive diagnoses based on Frascati criteria from baseline to two-year follow-up. Panel B: Change in neurocognitive diagnosis based on Frascati criteria from baseline to two-year follow-up. Panel C: Mean z-score by neurocognitive domain assessed at baseline and two-year follow-up; each spoke of the radar plot represents a cognitive domain, while spikes represents the magnitude of z-score changes per domain. The center of the plot represents the smallest (most negative) average change in z-scores we observed between baseline and follow-up (-0.5). ANI, asymptomatic neurocognitive impairment; MND, mild neurocognitive disease; HAD, HIV-associated dementia. Numbers are expressed in percentages.

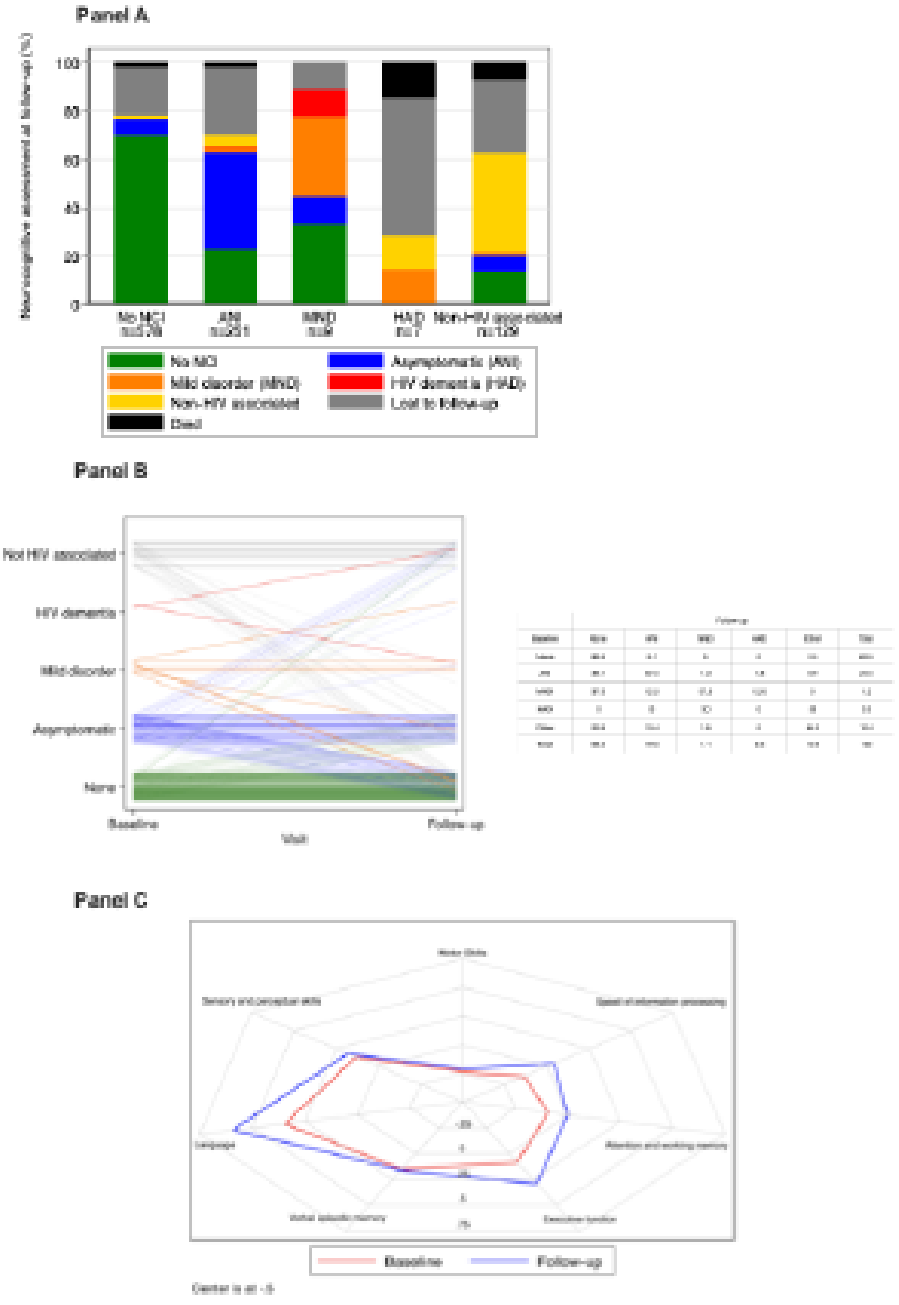

Figure 3. Clinical and demographic factors associated with neurocognitive change as measured by annualized mean z-scores between baseline and two-year follow-up in univariable and multivariable linear regression models. This figure corresponds to the data presented in supplemental, table 2, http://links.lww.com/QAD/C268. EACS, European AIDS Clinical Society; CES-D, Center for Epidemiological Studies Depression scale; CPE score, central nervous system penetration effectiveness score; ART, antiretroviral therapy.

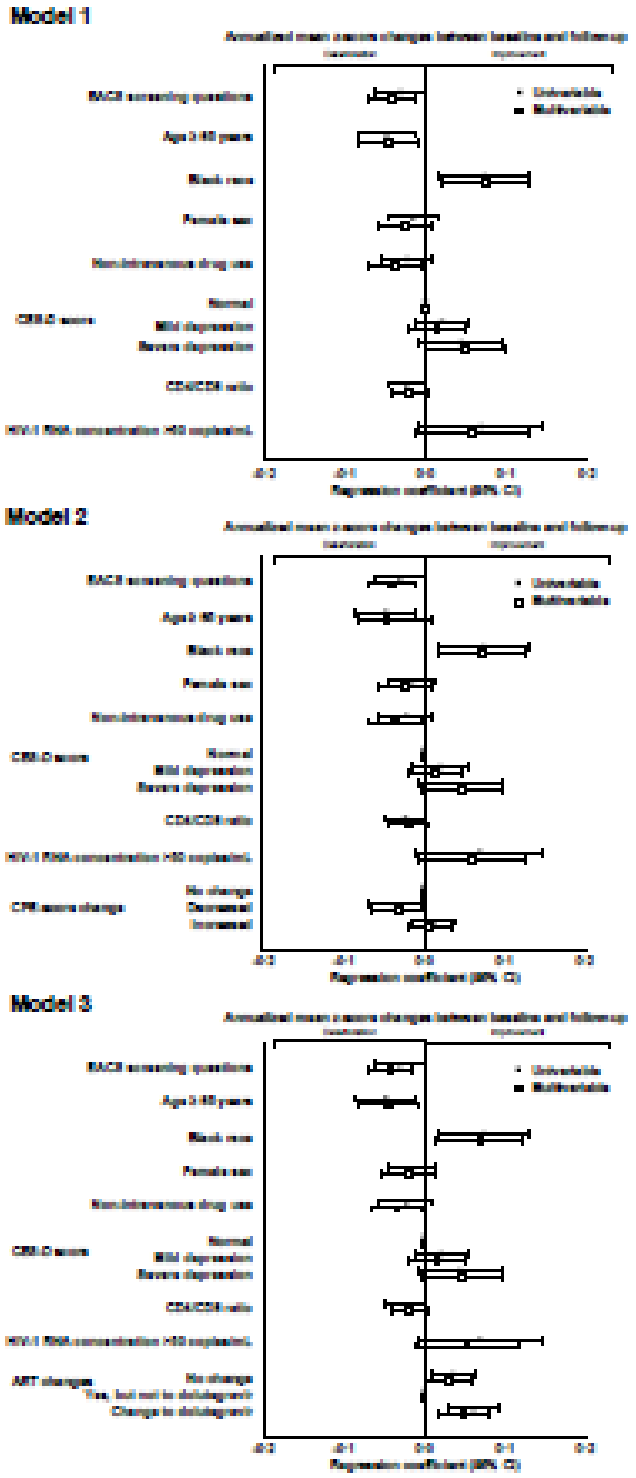

Table 1. Demographic characteristics, HIV acquisition mode and smoking, alcohol and drug use data for the 644 patients analyzed at baseline and two-year follow-up.

	Baseline (N=644)	**Follow-up (N=644)**	**p-value**
Median (range) age (years)	53 (49-58)	55 (52-61)	<0.001
Sex			
Female	124 (19.3%)		
Male	520 (80.7%)		
Race / Ethnicity			
White	595 (92.4%)		
Black	36 (5.6%)		
Asian	5 (0.8%)		
Latin American	8 (1.2%)		
HIV acquisition mode			
Heterosexual sex	191 (29.7%)		
Men who have sex with men	357 (55.4%)		
Intravenous drug use	75 (11.6%)		
Other	21 (3.3%)		
Education			1.0
Up to obligatory schooling	86 (13.4%)	86 (13.4%)	
Apprenticeship	316 (49.1%)	316 (49.1%)	
Secondary education	147 (22.7%)	147 (22.7%)	
Tertiary education	95 (14.8%)	95 (14.8%)	
Employment			0.01
No	169 (26.2%)	173 (26.9%)	
Yes	405 (62.9%)	366 (56.8%)	
Retired	70 (10.9%)	105 (16.3%)	
Smoke			0.55
Never	224 (34.8%)	221 (34.3%)	
Former	192 (29.8%)	209 (32.5%)	
Current	228 (35.4)	214 (33.2%)	

Alcohol consumption			0.24
None/mild	537 (83.4%)	552 (85.7%)	
Moderate/severe	107 (16.6%)	92 (15.3%)	
Current non-intravenous drug use	88 (13.6%)	98 (15.2%)	0.42
Current intravenous drug use	3 (0.4%)	4 (0.6%)	0.70

Data are median (IQR), or n (%). P-values obtained by the Pearson chi^2 or Fisher exact test for categorical variables, and by the Wilcoxon rank-sum non-parametric test for continuous variables.

Table 2. HIV-related, comorbidity and cognitive data for the 644 patients analyzed at baseline and two-year follow-up.

	Baseline (N=644)	**Follow-up (N=644)**	**p-value**
HIV-1 RNA >50 copies/mL	20 (3.1%)	4 (0.6%)	0.001
CD4 nadir (cells per μL)	174.5 (74-270)	174.5 (74-270)	1.0
CD4 count (cells per μL)	627.50 (464.5-807.5)	660 (500-870)	0.02
CD8 count (cells per μL)	707.50 (516.5-987)	710 (527-947)	0.76
CD4/CD8 ratio	0.89 (0.6-1.2)	0.92 (0.6-1.3)	0.05
Creatinine clearance (CKD-EPI)	87.22 (73.3-98.8)	78.2 (66.9-91.6)	<0.001
CPE score	7 (7-8)	8 (7-9)	<0.001
Treatment regime including Dolutegravir	18 (2.8)	196 (30.4)	<0.001
Comorbidities			
Cardiovascular disease	78 (12.1%)	83 (12.9%)	0.67
Metabolic disease	44 (6.8%)	46 (7.1%)	0.82
Liver disease	15 (2.3%)	18 (2.8)	0.59
Kidney disease	9 (1.4%)	9 (1.4%)	1.0
Bone disease	99 (15.4%)	107 (16.6%)	0.54

Hepatitis B	15 (2.3%)	15 (2.3%)	1.0
Hepatitis C	50 (7.8%)	29 (4.5%)	0.02
Toxoplasmosis	325 (50.5%)	325 (50.5%)	1.0
Cytomegalovirus	542 (84.2%)	542 (84.2%)	1.0
Syphilis (VDRL)	25 (3.9%)	29 (4.5%)	0.78
Depressive symptoms by CES-D scale			0.06
No symptoms	447 (69.4%)	476 (74.3)	
Mild depressive symptoms	136 (21.1%)	103 (16.1)	
Severe depressive symptoms	61 (9.5%)	63 (9.7)	
IADL	45 (6.9%)	36 (5.6%)	0.30
Neurocognitive domain affected			
Attention and working memory	182 (28.3%)	176 (27.3%)	0.70
Executive function	133 (20.7%)	96 (14.9%)	0.006
Language	36 (5.6%)	26 (4.1%)	0.14
Verbal episodic memory	104 (16.2%)	112 (17.4%)	0.60
Motor skills	239 (37.1%)	222 (34.5%)	0.32
Sensory and perceptual skills	22 (3.4%)	6 (0.9%)	0.001
Speed of information processing	193 (29.9%)	174 (27.0%)	0.24

Data are median (IQR), or n (%). P-values obtained by the Pearson chi^2 or Fisher exact test for categorical variables, and by the Wilcoxon rank sum non-parametric test for continuous variables. CKD-EPI, chronic kidney disease epidemiological collaboration; CPE score, central nervous system penetration effectiveness score; CES-D scale, Center for Epidemiological Studies Depression scale; IADL, Instrumental Activities of Daily Living.